

What are the Challenges to Developing Treatments for Charles Bonnet Syndrome?

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In this review, I will investigate the pathogenesis of the disease Charles Bonnet Syndrome (CBS). CBS is a condition that involves complex hallucinations that aren't disturbing to a patient's everyday life, but rather just visual images that tend to vary from patient to patient. The hallucinations that patients experience are incredibly distinct. Patients tend to see overlapping patterns, multiple forms of one image, and facial distortion. CBS involves several cortexes of the brain that are responsible for our vision and the hallucinations that patients see. CBS is classified under a separate category of hallucinatory induced conditions due to the quality of the hallucinations, patient background and rarity of occurring in a population, as well as what is responsible for onset of the condition. Schizophrenia, for example, has a median value of 15.2 per 100,000, which may appeal less, however, it is a major contributor to worldwide disease and is more common to occur during young adulthood around 20-30. Dementia interferes with daily activity and around 24.3 million people have dementia today with 4.6 million new cases every day. CBS, on the other hand, is a much rarer condition as it has been reported only 10%-15% in visually impaired older adults (which is the most common patient background for the condition). CBS hallucinations are classified as "psuedohallucinations" because patients are aware they are experiencing hallucinations rather to schizophrenia and dementia that aren't aware of them. The current medical field is unable to determine a certain demographic percentage of patients with CBS because it is a condition diagnosed under different fields, and many patients struggle to report the condition themselves. Therefore, tracking this condition is difficult in a numerical sense. Many researchers display results of medicines that fall under the broad category of hallucinations without further research to specifically target CBS because of the lack of knowledge pertaining to the condition. There's a disparity in findings from researchers due to confounding variables in their experimental groups. Patients that experience hallucinations can be influenced by many factors which is why researchers are aware that the causes that they discover could concern a specific case rather than a generalized population.

Keywords: Illegal dumping, COVID-19, Waste Management, Philadelphia.

Introduction

CBS was first discovered in 1769, when Charles Lullin, Charles Bonnet's grandfather suffered from symptoms of the disease as he was hallucinating visions of birds, people and buildings. Despite this, most experiments and studies on the condition date from the 21st century¹.

Methodology

Compilation of information was through an analysis of 30-40 papers with differentiating findings, and important information corresponding to each other were built to discuss patterns of gaps in research studies and pathology of CBS. The main resources of information of this literature are comprised on papers from Google Scholar and PubMed. The research papers are case studies and small experiments of CBS which categorize the findings of their studies into neurological, optical, and external factors.

Studies use correlational data and graphs, brain image scanning as well as tables of patient data to reference information in their results. Reinforcing research papers for background information of conditions such as schizophrenia, and dementia were used to accurately compare CBS. Papers researching specific regions of the brain were also utilized to properly discuss function and how their disruption can induce hallucinations. These papers are recently ranging from 2005-2019 in publication.

Causes and Symptoms

Hallucinations are the clearest indicator of CBS, as well as time span of experiencing them. Completely varying from patient-to-patient hallucinations can last seconds, minutes or hours and also perceive a diversified range of hallucinations. This condition lacks a reliable diagnostic signature, depending on subjective information from patients rather than the technology at current disposal.. Types of psuedohallucinations that some pa-

tients experience aretesellopia (regular, overlapping patterns), prospometamorphopsia (facial distortion), dendropsia (branching forms), hyperchromatopsia and polyopia (multiple forms of one image), micropsia and macropsia². According to one article, CBS associates with several eye conditions that mostly occur in elderly people such as macular degeneration, choroidal degeneration—which affect the choroid, a layer of connective tissue and blood vessels in the eye—choroidal neovascularization, and homonymous hemianopia—vision loss caused by brain damage—with a 27% chance of this correlation¹. Vale et al present aligning findings of eight patients with varying ophthalmological diseases and their significance in relation to CBS. They claim that while macular degeneration is the strongest correlational cause, there are other eye conditions that can also cause CBS². One study states that the loss of visual acuity is an important factor that creates the onset of CBS. It states the common rate of patients with a greater visual acuity of 12% rather than a lower visual acuity boosts the prevalence rate to 28%. Age is a likely cause of CBS as well, patients have a mean age of 70 to 85, and another study determines a mean age of 74.5 out of six Brazilian patients (Brucki et al.). Some external circumstances that have a correlation with this disease are social isolation and dimly lit conditions². According to an experiment testing the effect of isolation caused by COVID-19 on CBS hallucinations there was a strong correlation between the feelings of loneliness caused by social isolation and the hallucinations that occurred in the subjects³. Overall, there seems to be a combination of causes of CBS and as they are widely varying, there doesn't seem to be many strong correlations between these causes and symptoms in CBS. In every study everyone gets different results

Current Pathogenesis

CBS symptoms connect the optical and neurological systems in several ways. Therefore, it's hard to accurately pinpoint what is directly causing this condition to occur, as there are many different studies with a variety of findings. One of the very few longitudinal studies called the SHAPED trial (Study of Hallucinations in Parkinson's Disease (PD), dementia, and eye disease) consisted of questionnaires and interviews for patients with these conditions for practitioners to continue with procedures of how to approach these conditions. The findings were 75% of patients with eye disease experienced simple hallucinations, and 25%-30% for PD and dementia. Out of this small percentage, doctors had to select patients that had backgrounds of being elderly, visually impaired, and isolated as main factors of vulnerability to CBS. This exemplifies how the diagnosis is very hindered due to the limited knowledge of the complex aspects causing CBS and miniscule condition prevalence. However, researchers attempt to deduce differentiating findings of what induces CBS to occur.

First, Carpenter et al believe that cortical hyperexcitability, ex-

tensive activity in the cerebral cortex, may be a factor for some CBS patients. When the cerebral cortex, which is responsible for cognitive function, sensory perception and various other functions, is excited, it leads to an imbalance in the inhibitory signals of the brain which can lead to the visual stimuli being interpreted as hallucinations. Conversely, they also have found information regarding the responsibilities of visual sensory inputs, which are vision stimulus, and contain inhibitory pathways that ensure proper visual perception and preventative measures of overload and distortion of visual information that is to be processed. CBS can cause these sensory inputs to suppress, which impact the feedforward and feedback connections in the brain which are dependent on the sensory inputs. These connections are incredibly complex and interconnected which also have fine-tuned functions that each influence each other to modify signal processing⁴. Therefore, with the reduction of sensory input in the feedback input in the feedforward connections, it leads to receipt of feedback signals from other areas of the brain that can possibly lead to CBS hallucinations in patients leading to a lack of acetylcholine—a neurotransmitter responsible for muscle contraction, memory, learning and attention¹. This finding is plausible because a lack of acetylcholine neurotransmitter leads to Alzheimer's disease. This shows how CBS hallucinations experienced by patients from this cause can be induced by similar neurotransmitters regardless of the type of hallucination condition.

Findings also mention patients that experience CBS hallucinations had abnormalities, which were basilar and posterior cerebral arteries of the brain. The basilar artery is divided into branches of posterior cerebral arteries that then direct blood supply to the thalamus and occipital lobes of the brain. These abnormalities have a significant effect on hallucinations due to the processes of blood flow and responsibilities of these different areas of the brain corresponding to vision. As we process visual stimuli in our retina, they are sent to the thalamus—responsible for directing various sensory stimuli to the different parts of the brain associated with each type of stimuli—which are then sent to the occipital lobe which processes these visual stimuli into interpreting the images that our eyes see. An abnormality in the arteries that provide function to these parts of the brain can hinder accurate interpretation of visual stimuli which is what leads to these hallucinations to occur in patients. These compiled studies emphasize the neurological etiology of what causes CBS to be supported by how the occipital lobe and its counterparts play a crucial role in the onset of the condition for many patients. However, these theories don't consider the overlooked brain activity occurring in other patients, ophthalmological factors or also the external factors that can also induce this condition.

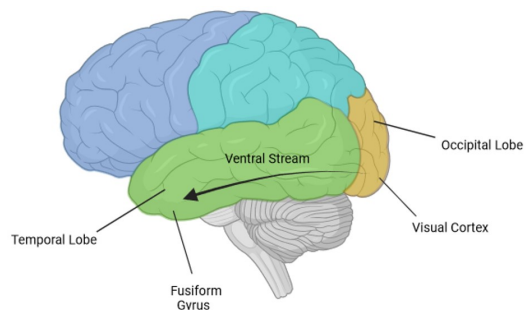
To begin with, there are studies that support the findings of other parts of the brain responsible for these visual hallucinations rather than just the occipital lobe and its supporting areas of the brain. The visual ventral stream process that enables object

recognition through linking visual input to memories primarily made of the occipital and the temporal lobe—is also a prevalent factor in patients experiencing hallucinations. Carpenter and Vale et al, both mention that groups of CBS patients exhibited increased blood flow and overactivity in the striatum, lateral temporal cortex, and thalamus^{1,2}. This increased blood flow is because all 3 of these brain regions work together to execute the function of the visual ventral stream. Specifically, in this stream, the striatum controls reactions to what we interpret from visual stimuli in our occipital lobe, and the lateral temporal cortex is responsible for object and facial recognition and other types of complex processing. This helps explain how regions of the brain that aren't associated with vision are connected to regions of the brain that executive visual functions.

On the other side of the spectrum, studies conducted by Heron and colleagues found that a deprivation of sensory stimuli can lead to vivid hallucinations (e.g devils, cops, Christmas tree lights etc.). This is due to the brain's responsibility to fill in missing "holes" in our perception because its job is being ceased. This leads to the brain creating its own stimuli to compensate for the lack of actual stimulus leading to hallucinations. The brain's ability to compensate for a lack of proper sensory stimulation can be what leads to sensory inputs, inhibitory pathways and abnormal brain function to occur, otherwise known as the Deafferentation Theory. Furthermore, compared to all of these neurological aspects of what can cause CBS, various optical factors must also be taken into consideration that are supported by studies as well. First off, an optical study with CBS provides the theory that the bilateral loss of vision is a strongly correlated factor with the development of CBS. The researchers used Snellen chart (rows of 5 letters that get smaller in size to test vision, and it is the most common vision testing method using in optometry) and ETDRS chart (specialized vision testing for retinopathy issues involving a logarithmic progression of letter size) to assess visual acuity; researchers also used the Heidelberg Eye Explorer, which utilizes various analytic tools to assess how vision loss contributes to CBS, and Spectral - Domain Optical Coherence (SD-OCT) — cross-sectional imaging of the retina that is non-invasive. The study was able to identify that geographic atrophy, macular degeneration of the retina cells in the eye, was more prevalent in CBS patients compared to non-CBS patients. Figure 2 illustrates the location of the retina and how it can impact other parts of the eye that relay visual stimuli. Another finding was that geographic atrophy positively correlates with inner and outer segments (IS/OS lines of retina photoreceptors) integrity. Photoreceptors consist of rods and cones that help us perceive color and shape, as shown in Figure 3, they assist the retina in stimulus transmission. The existence of these correlations in the anatomy of the eye still cannot pinpoint the exact optical cause of CBS. The study was able to determine that deterioration of our overall vision plays a big factor and can only ensure that geographic atrophy is a reason for CBS⁵. External factors, op-

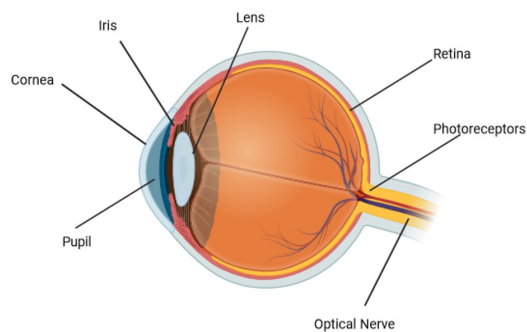
tical factors, and dispersal of regions of the brain responsible for CBS are all interconnected when it comes to interpreting stimuli, and the fact that if one part of the brain is affected all other parts of the brain and optical systems become affected as well. Also, external factors can hinder processes of the eye or the brain and can lead to this effect as well. This explains why every study tends to find different results through their own experiments because of this. Therefore, a consensus of what is driving factor to CBS is lacking in our society because the current experiments don't eliminate these confounding variables and focus on certain variables in what causes CBS.

The basilar artery provides blood for parts in the back of the brain such as the brainstem and cerebellum which are associated with autonomic function and balance. The posterior cerebral artery provides oxygenated blood to the occipital lobe which is the lobe of the brain that receives and interprets neural signals from the optical system⁶.



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Fig. 1 The schematic presents the most common areas of the brain that are hyperactive during hallucinations of CBS. (Made with Biorender)



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Fig. 2 The schematic presents the parts of the eye that assist in visual stimuli reaching the retina and optical nerve for occipital lobe processing. (Made with Biorender)

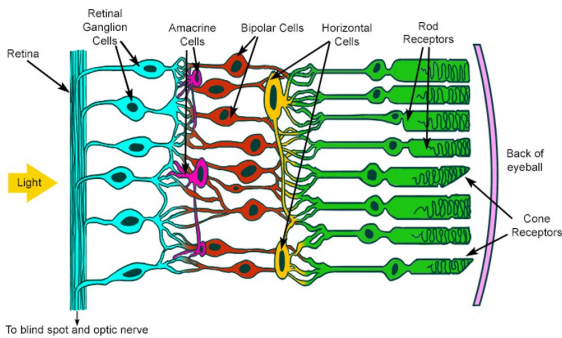
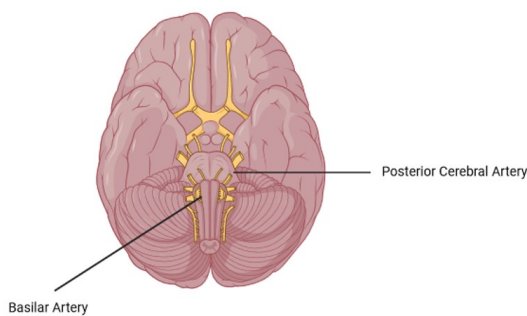


Fig. 3 The schematic presents a more specified process of cells behind the retina that process color, shape and detail of visual stimuli for the thalamus to direct to the occipital lobe to process. (Made with Biorender)



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Fig. 4 The schematic presents location and visual representation of supporting regions of the brain that support the occipital lobe in the process of interpretation of visual stimuli. (Made with Biorender)

Treatment

The treatment pertaining to CBS is diverse across a field of many studies because each study has tested different pharmacologic agents, procedures, patient empathy, and therapy. A case report by Schadlu et al. states how administering 5 mg/day of antipsychotic olanzapine — used to treat medical conditions such as schizophrenia by affecting dopamine and serotonin activity — had a success rate of removing hallucinations over the course of 7 days. The patient was slowly removed from the medicine and returned to hallucinating 3 months later. A differing case report has findings of how donepezil — treats Alzheimer’s and types of dementia by increasing acetylcholine levels in the brain — mitigated symptoms for a span of 40 months⁷. Even within these studies that are focused on medication for treatment, there isn’t a streamlined encompassing study to identify which medication works through thorough experimentation with studies such as double blind, or placebo testing. On the other hand, a completely outlying study discusses how 92-year-old woman experienced CBS hallucinations primarily due to hypoxemia and oxygen

saturation levels among her other conditions such as macular degeneration, atrial fibrillation, and left ventricular hypertrophy. The patient experienced a low nocturnal arterial oxygen saturation (SaO₂) of 78% (normal <89%) and 184 minutes spent with SaO₂ below 90% overnight — oxygen levels measured during sleep to measure sleep apnea — The patient administered oxygen supplementation at a flow rate of 3 L/min and it led to a reduction in nocturnal hypoxemia, and consequently hallucinations ceased after 2 days. A commonality of all the researchers across the multidiscipline of studies states how empathy and reassurance are the most reliable way to approach this disease at the current moment. According to a study, 16/17 (94%) of patients felt more comfort and believed it was the most useful to them as they were experiencing CBS². Among all these treatments for CBS, such as drugs that are typically used for other hallucinatory conditions, therapies, patient care, and supplementation techniques there is one true reason for the variety of why success differs for each treatment among patients. It is because each patient that experiences the onset of CBS is due to a variety of main causes of the condition. One patient may experience this condition due to disrupted neurological activity, but another may get CBS because of ophthalmological problems, or maybe even because of the function of the human body because of age. It’s hard for doctors to be able to specify which approach to take because the cause is so differentiative among patients which is why we don’t know much about what causes CBS overall in majority of patients. This uncertainty also stems from the different imaging techniques utilized by researchers. Every case is due to a different factor; therefore, researchers need to use the best imaging to identify etiology, but this poses a complication. Each imaging technique displays different results because each one has a distinct role to one another. This obscures comparison among findings and the ability for research to build upon another’s findings for solutions. In other words, there are inconsistencies among the physiological and neurological causes of the conditions, making it hard to draw strong conclusions. These factors all contribute to an interconnected web pertaining to the lack of knowledge of CBS pathology. Researchers can’t diagnose specific pathology, which leads to uncertainty about pharmaceutical agents that prove effective as we can’t pinpoint which medicine will target the hallucinations. This in summary, all causes the lack of what causes CBS pathologically and a optimal solution as well.

Purpose of Research

The research on CBS shows the causes of it are largely varying; and each study proposes their own effective solution to treating the disease. Carpenter et al describe Charles Bonnet Syndrome to be caused by dysregulation in several regions in the brain. Another paper states the association of the visual association cortex causing disinhibition and spontaneous firing of the visual

cortex regions, the emotions playing a role in hallucinations in the disease and agrees with the hyperperfusion of certain parts of the brain causing this disease as well as social isolation and age playing a factor. Another study mentions how depending on the patient's different parts of the brain can be causative of this condition⁸. All these papers have different study sample sizes and control groups. All of these papers do have commonalities in discovery that give us a broad idea of this condition. In many studies conducted on CBS, every patient has different backgrounds, and the methods used to study lead to different overall diagnostic signatures. Sample sizes for studies on CBS patients are very low. Kazui et al describe a study method of participants and in a study mentioning Japanese Herbal tea as a treatment, the sample size was 20 patients¹. Many of the claims and theories formed from the study of this disease are based on these experiments. This doesn't accurately represent the CBS population or provide enough data points to grasp a deeper understanding of the disease. Jones et al. mention the social implications of COVID-19 on CBS, using a sample size of 45 respondents over a period of 31 days³. Another paper studying the neurological processes of hallucinations focused on two cases and used the information extracted from those patients to describe the intricate hallucination results⁸. These examples highlight the unrepresentative research into CBS that led to flaws in its diagnosis and treatment. In comparison, other studies of more common psychological disorders such as schizophrenia have much bigger sample sizes, due to it being a much more common disease, making it easier to obtain a representative sample size for studies. An example paper highlighting this point is a study of schizophrenia that looked at 31 Finland families and detected the rates of the condition, genes responsible, with high statistical significance⁹. Overall, the studies that have been utilized to study CBS lack a high number of participants and are rather case studies and very small experiments which concomitantly leave inconsistencies in the pathogenesis of the disease. In addition, longitudinal studies are lacking pertaining to this condition. Longitudinal studies are the most useful studies because researchers can track the progression of patient background and correlate what is causing hallucination to occur in patients and tailor treatments through these correlations. As a society, out of curiosity and necessity for the cure of this disease, there have been many studies done to research the direct causes concomitant with the hallucinations. Some of these examples in our more recent time period are "Exacerbation of visual hallucinations in CBS due to social implications of Covid-19", this is a very recent case study from 2020 where the implications of social isolations influence CBS patients on a neurological basis³. In the more recent studies such as Carpenter et al, Kazui et al, and Vale et al, they make use of the most advanced technology at our disposal, including MRI and fMRI. At this point in time, we can directly identify anatomically what parts of the brain are causing the condition in specific patients and describe this in detail but

not pinpoint the cause. The current brain imaging technology can't isolate the specific brain segments causing the disease and non-physiological confounding variables that can cause these hallucinations. This limitation is very hindering because studies can't correlate which parts of the brain experience abnormalities, as well as each technology yielding different results. These studies that utilize the current imaging technology at disposal can procure inaccurate and inconclusive results. Results can yield different parts of the brain being hyperactive, and others not, however another brain scan could be determined differently leading to researchers building on inconclusive and inaccurate data. An example of this a case study by Kazui et al in the diagnosis of an elderly woman experiencing hallucinations and eye problems. The results yielded no abnormal occipital lobe activity using cerebral MRI and low-amplitude fast waves, however nothing indicating epilepsy⁸. In summary, the many mysteries shrouding the causation of these hallucinations of CBS is due to the lack of technology and experimental research to back up theories of the condition. We cannot overall comprehend the disease yet and that is what makes this condition interesting and important to report on. Another problem is highlighted in Kazui et al. Many studies used to determine brain activity using many different types of brain scanning techniques (e.g. fMRI, Magnetoencephalography, SPECT). One study evaluated neuroimaging via region cerebral blood flow with SPECT (nuclear imaging that identifies blood flow activity) and occipital lobe activity was normal⁸. These results contradict from the earlier findings that state that the middle fusiform gyrus (Fig 1) activity was displayed in other studies. Overall, the type of technology used to determine CBS neurology is inconsistent throughout multiple studies in this paper, which is another factor that concerns research on this condition. This ties with another main issue with CBS which is how many different studies are getting contradicting results. We get a surface level of symptoms and understanding of CBS, but we can't dive into any deeper analysis due to so many confounding variables that obstruct further knowledge of this disease. Every study mentioned in this paper has done research on very small sample sizes (which is very unrepresentative of the population). In addition, external circumstances like age, social isolation, previous eye condition history etc. need to be considered. Finally, what is missing is how the current technology we have isn't able to pinpoint at a high enough resolution the specific brain segments correlating with the hallucinations.

Future Avenues

There are many different medications and alternative medical solutions that don't involve traditional practice and treatment like (CAM) therapy options that have been tested and used by many different doctors for CBS. However, doctors are unable to properly offer the right options for treating CBS, therefore

many medical professionals offer solutions pertaining to more renowned and diagnosed hallucination conditions. CBS can be lifelong, or it can resolve over time so there are different mechanisms to ease the symptoms patients may experience. However, there isn't a clear and direct route for stopping the hallucinations altogether. Common general eye exercises recommended by patient groups and charities are for a variety of conditions involving hallucinations and hence support the point that we currently don't know what is triggering these hallucinations and what is specifically causing them. That is why this pattern will emerge among many different charity websites and condition information. Talking to people you trust and depending on CBS organizations is a common theme mentioned in many papers because of the magnitude of this disease on people's livelihood which all concludes our lack of understanding of CBS. On the research paper side, there is a more specific and technical approach to dealing with this condition. Schadlu et al suggest focusing on the external factors that have an impact on this disease such as visual function, social isolation and empathy and support from physicians and ophthalmologists toward patients with this disease⁷. "Elephant in the Room" suggests focusing our attention on the visual cortex, the factor of age and understanding the more common hallucination disorders for CBS due to annexation of the hallucination factor itself¹. Much other research aligns with these views of how to continue and advance towards the diagnosis of CBS. There are a few future avenues that I believe that the diagnosis of CBS should gravitate towards. The first is focusing on the most common patient backgrounds that are associated with CBS.

This would mean running experiments on an elderly group with common eye conditions that are known to pair with CBS, as well as testing separate environmental factors. Using MRI and fMRI, we can detect blood flow and activity in the brain and assess what has the most effect. It is important to make sure that each of the patients with similar backgrounds are in the same group so confounding variables don't influence this study. Another important part is to make sure factors such as social desirability bias and representative sample are included in the study. Another effective way to continue to do this is to start a meta-analysis of the current external factors that are known to influence CBS and get a better understanding of them in the context of other diseases as well. Running longitudinal studies on different types of prescriptions and medicine on patients can be an ideal strategy. The people being experimented on should be following the basic guidelines regarding common external circumstances to avoid that cause CBS such as social isolation, and lighting to maximize the potential of the study. On the pharmaceutical side, addressing the lack of studies to be able to determine among which medicines work best among a more generalizable population is a great way to prevent patients from experiencing CBS. Researchers can run trials of a wide variety of medicines in patients grouped by specific factors such

as social isolation, or vision problems and then categorizing medicine testing based on these factors. Ethically, though, as we evolve it is important for medical facilities to be welcoming towards patients that display hallucinations because of the factor of patients in denial of the hallucinations in the first place. Many patients are scared to admit they hallucinate which is hindering studies from having larger study samples and doctors understanding the prevalence of CBS so we can continue to diagnose the disease.

Conclusion

CBS is an ophthalmological and neurologically induced condition that differs from other diseases because of patients' mental states staying intact while experiencing hallucinations. The hallucinations are easy to identify for patients and are very detailed in the patient's perspective. The onset of CBS is mainly associated with deteriorating visual acuity, and old age. There are many other variables and tested factors that influence the hallucinations such as social isolation and correlation with other eye conditions but can't be completely proven. The current standing etiology of what causes CBS is difficult because every paper discusses different prevalence of anatomy of what is responsible for the condition. Different researchers observed varying symptoms. This discrepancy in these findings arises from the sample populations used in testing, and every patient differing from each other pertaining to their environmental stimulus, patient background, and genetics. The lack of longitudinal studies to track progression of the condition in CBS leaves huge gaps of knowledge in CBS etiology and its disparity. These are a collection of all the challenges to developing treatments for CBS. Overall, the inability of researchers and doctors to diagnose what is specifically causing the condition leads to estimations and dependence on subjective info from the patient's perspective which makes current treatment unreliable and proceeding with further treatments difficult.

As a society, however, to diagnose the etiology of CBS and proceed with treatment is through avenues such as patient comfort, utilization of longitudinal studies, and improving experiment procedures by using larger sample sizes and eliminating confounding variables. These future avenues can combat the paucity of pharmaceutical treatments for CBS by creating correlational trends and getting much more neurological and optical data to tailor treatment towards in patients. Nevertheless, the most important part is ethical and maintain empathy towards patients to be able to welcome people struggling with hallucinations and spread awareness of CBS in our society.

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